Exhibit 5

Docket No.: A1025.70048US00
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor:	Erin Anne Kimbrel
Application No.:	13/905,526
Confirmation No.:	7854
Filed:	May 30, 2013
For:	MESENCHYMAL STROMAL CELLS AND USES RELATED THERETO
Examiner:	A. M. Ford
Art Unit:	1653

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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: November 26, 2014 Signature: /Melissa Simpson/ (Melissa Simpson)

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

INTRODUCTORY COMMENTS

In response to the Restriction Requirement dated May 27, 2014, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

Please replace all prior versions and listings of claims in the application with the following listing of claims.

1.-105. (Canceled)

106. (Currently Amended) A method for treating a disease or disorder, comprising administering to a subject in need thereof an effective amount of mesenchymal stromal cells or a preparation of mesenchymal stromal cells obtained by a method comprising culturing hemangioblasts under conditions that give rise to mesenchymal stromal cells. ~~according to claim 83 to a subject in need thereof.~~

107. (Previously Presented) The method of claim 106, that further comprises the transplantation of other cells or tissues; or that further comprises the transplantation of retinal, RPE, corneal, neural, immune, bone marrow, liver, or pancreatic cells.

108. (Canceled)

109. (Currently Amended) The method of claim 106, wherein the disease or disorder is selected from multiple sclerosis, systemic sclerosis, hematological malignancies, myocardial infarction, organ transplantation rejection, chronic allograft nephropathy, cirrhosis, liver failure, heart failure, GvHD, tibial fracture, left ventricular dysfunction, leukemia, myelodysplastic syndrome, Crohn's disease, diabetes, chronic obstructive pulmonary disease, osteogenesis imperfecta, homozygous familial hypocholesterolemia, treatment following meniscectomy, adult periodontitis, vasculogenesis in patients with severe myocardial ischemia, spinal cord injury, osteodysplasia, critical limb ischemia, diabetic foot disease, primary Sjogren's syndrome, osteoarthritis, cartilage defects, multisystem atrophy, amyotropic lateral sclerosis, cardiac surgery, refractory systemic lupus erythematosis, living kidney allografts, nonmalignant red blood cell disorders, thermal burn, Parkinson's disease, microfractures, epidermolysis bullosa, severe coronary ischemia, idiopathic

dilated cardiomyopathy, osteonecrosis femoral head, lupus nephritis, bone void defects, ischemic cerebral stroke, after stroke, acute radiation syndrome, pulmonary disease, arthritis, bone regeneration, inflammatory respiratory conditions, respiratory conditions due to an acute injury, Adult Respiratory Distress Syndrome, post-traumatic Adult Respiratory Distress Syndrome, transplant lung disease, Chronic Obstructive Pulmonary Disease, emphysema, chronic obstructive bronchitis, bronchitis, an allergic reaction, damage due to bacterial pneumonia, damage due to viral pneumonia, asthma, exposure to irritants, tobacco use, atopic dermatitis, allergic rhinitis, hearing loss, autoimmune hearing loss, noise-induced hearing loss, psoriasis or any combination thereof.

110. (Previously Presented) The method of claim 106, wherein the disease or disorder is uveitis, an autoimmune disorder, an immune reaction against allogeneic cells, multiple sclerosis, bone loss, cartilage damage, or lupus.

111.-125. (Canceled)

126. (New) The method of claim 106, wherein the mesenchymal stromal cells

(a) are mitotically inactivated;

(b) have replicative capacity to undergo at least 10 population doublings in cell culture with less than 25 percent of the cells undergoing cell death, senescing or differentiating into non-MSC cells by the tenth doubling;

(c) have replicative capacity to undergo at least 5 passages in cell culture;

(d) have replicative capacity to undergo at least 5 passages in cell culture with less than 25 percent of the cells undergoing cell death, senescing or differentiating into fibroblasts by the 5^{th} passage;

(e) are HLA-genotypically identical; and/or

(f) are genomically identical.

127. (New) The method of claim 106, wherein the preparation of mesenchymal stromal cells comprises at least 10^6 mesenchymal stromal cells and less than one percent of any other cell type,

wherein the mesenchymal stromal cells have replicative capacity to undergo at least 10 population doublings in cell culture with less than 25 percent of the cells undergoing cell death, senescing or differentiating into non-MSC cells by the tenth doubling.

128. (New) The method of claim 106, wherein

(a) at least 30% of the mesenchymal stromal cells are positive for CD10; and/or

(b) at least 60% of the mesenchymal stromal cells are positive for markers CD73, CD90, CD105, CD13, CD29, CD44, CD166 and HLA-ABC; and/or

(c) less than 30% of the mesenchymal stromal cells are positive for markers CD31, CD34, CD45, CD133, FGFR2, CD271, Stro-1, CXCR4 and TLR3.

129. (New) The method of claim 106, wherein

(a) at least 50% of the mesenchymal stromal cells are positive for all of CD10, CD24, IL-11, AIRE-1, ANG-1, CXCL1, CD105, CD73, CD90, CD105, CD13, CD29,CD 44, CD166, CD274, and HLA-ABC; and

(b) no more than 30% or no more than 10% or no more than 5% of the mesenchymal stromal cells are positive for CD31, CD34, CD45, CD133, FGFR2, CD271, Stro-1, CXCR4 or TLR3.

130. (New) The method of claim 106, wherein the mesenchymal stromal cells

(a) have replicative rates to undergo at least 10 population doublings in cell culture in less than 25 days; and/or

(b) have a mean terminal restriction fragment length (TRF) that is longer than 8kb; and/or

(c) have a statistically decreased content and/or enzymatic activity, relative to mesenchymal stromal cells derived from bone marrow that have undergone five population doublings, of proteins involved in one or more of (i) cell cycle regulation and cellular aging, (ii) cellular energy and/or lipid metabolism, and (iii) apoptosis; and/or

(d) have a statistically significant increased content and/or enzymatic activity of proteins involved in cytoskeleton structure and cellular dynamics relating thereto, relative to mesenchymal stromal cells derived from bone marrow; and/or

(e) do not undergo more than a 75 percent increase in cells having a forward-scattered light value, measured by flow cytometry, greater than 5,000,000 over 10 population doublings in culture; and/or

(f) in a resting state, express mRNA encoding interleukin-6 at a level which is less than ten percent of the IL-6 mRNA level expressed by mesenchymal stromal (IL-6) cells, in a resting state, derived from bone marrow or adipose tissue; and/or

(g) induce a 40% or greater decrease in T-cell activation compared to mesenchymal stromal cells derived from bone marrow or adipose tissue; and/or

(h) induce an increased regulatory T cell (Treg) induction and/or expansion compared to mesenchymal stromal cells derived from bone marrow or adipose tissue.

131. (New) The method of claim 106, wherein the mesenchymal stromal cells have a potency in an immune regulatory assay greater than the potency of bone marrow derived mesenchymal stromal cells.

132. (New) The method of claim 131, wherein the potency is assayed by an immune regulatory assay that determines an EC50 dose.

REMARKS

Claims 46, 47, 49, 58, 61, 63, 66-67, 72-74, 82, 83, 85, 94, 106, 107, 109, 110 and 116 were previously pending in this application. By this amendment, claims 46, 47, 49, 58, 61, 63, 66, 67, 72-74, 82, 83, 85, 94 and 116 are canceled without prejudice or disclaimer as being drawn to non-elected subject matter. Claim 106 has been amended without prejudice or disclaimer. Claims 126-132 are new. Support for the amended and added claims can be found throughout the specification and claims, as originally filed. As a result, claims 106, 107, 109, 110 and 126-132 are pending, with claim 106 being an independent claim. No new matter has been added.

Examiner Interview Summary

Applicant's representatives, the undersigned and Maria A. Trevisan, conducted a telephone interview with the Examiner on October 1, 2014. Possible elections and claim amendments were discussed during the interview. The undersigned thanks the Examiner for the opportunity to discuss this restriction requirement.

In response to the Restriction Requirement mailed May 27, 2014, Group II is elected for continued examination. The following species are also elected:

Election 1 – Lupus

Election 2 – In view of the election of lupus, Applicant requests withdrawal of this species election. When treating lupus, the method of claim 106 may not involve transplantation of other cells or tissues.

These combined elections embrace at least claims 106, 109, 110 and 126-132.

These species elections are made with the understanding that they are required for search and examination purposes only and that, upon the allowance of a generic claim, claims to additional species, which depend from or otherwise require all the limitations of the allowed generic claim as provided by 37 CFR 1.141, will be considered. The right to file one or more continuing applications on the subject matter of the non-elected claims is expressly reserved.

Applicant submits herewith a Petition for a Four-Month Extension of Time and payment of the required fee. With this extension, a reply is due on or before November 27, 2014.

If there is an additional fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. A1025.70048US00 from which the undersigned is authorized to draw.

Dated: November 26, 2014

Respectfully submitted,

By /Katherine Miller/
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